First Synthesis of Double Headed 1,2,4-Triazino[5,6-*b*]indole Acyclo *C*-Nucleosides

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Heterocyclization of bis(2-oxo-indol-3-ylidene)-galactaric acid hydrazide (**3**) with a variety of one-nitrogen cyclizing agents gave the corresponding 1,4-bis{1,2,4-triazino[5,6-*b*]indol-3-yl}-*galacto*-tetritols **4-8**. Acetylation of the latter double headed acyclo *C*-nucleosides with acetic anhydride in the presence of pyridine at ambient temperature resulted in N- and O-acetylation to give the corresponding 1,2,3,4-tetra-*O*-acetyl-1,4-bis{1,2,4-triazino[5,6-*b*]indol-3-yl}-*galacto*-tetritols **9-13** which were found to exist in centro-symmetric zigzag conformations **20**. The assigned structures were corroborated by ^{1}H, ^{13}C NMR as well as mass spectra.

Keywords: Bis(2-oxo-indol-3-ylidene)-galactaric acid hydrazide; One-nitrogen cyclizing agents; Heterocyclization; Double headed 1,2,4-triazino[5,6-*b*]indole acyclo *C*-nucleosides.

INTRODUCTION

The synthesis of 1,2,4-triazino[5,6-*b*]indoles has been surveyed in three reviews.[1-3] A large number of compounds belonging to this ring system were extensively synthesized from both research and medicinal chemistry points of view. The incorporation of certain functional groups into the skelton of this ring system may yield a compound with enhanced biological activities. Thus, 3-hydrazino- and 3-thiosemicarbazido- derivatives of 1,2,4-triazino[5,6-*b*]indoles have been found to possess antimicrobial,[4-8] antiviral,[9] antihypertensive,[9,10] blood-platelet aggregation inhibitory,[10,11] and analgesic[12] activities. In addition, 3-arylidene- and 3-alditol-1-ylidenehydrazino-1,2,4-triazino[5,6-*b*]indoles showed antitumor activity against P388 lymphocytic leukemia in mice[13] and antibacterial activity.[14,15]

On the other hand, the chemistry of acyclo *C*-nucleosides have been reviewed[16-22] and valuable medicinal applications and biological activities have been found to be associated with acyclo *C*-nucleosides carrying various types of heterocycles due to their ability to mimic isosteric *N*-nucleosides. Various synthetic members of acyclo *C*-nucleosides have been reported to be useful as antivirals,[23] antibacterials,[24] antifungals,[25] protein kinase inhibitors,[26] lymphopenia producers[27] and diagnostic markers for cancer.[28] Moreover, pharmaceutical applications including the treatment of some metabolic diseases such as Parkinson's disease[29] have been attributed to some acyclo *C*-nucleoside precursors. Despite all these highly desirable activities and medicinal applications, and to the best of our knowledge, the incorporation of a tetritolyl moiety to 1,2,4-triazino[5,6-*b*]indoles has not been reviewed. Consequently, the goal in the present work is to develop the first synthesis of the double headed 1,2,4-triazino[5,6-*b*]indole acyclo *C*-nucleosides as a part of our studies on the synthesis of acyclo *C*-nucleosides.[14,25,30-33]

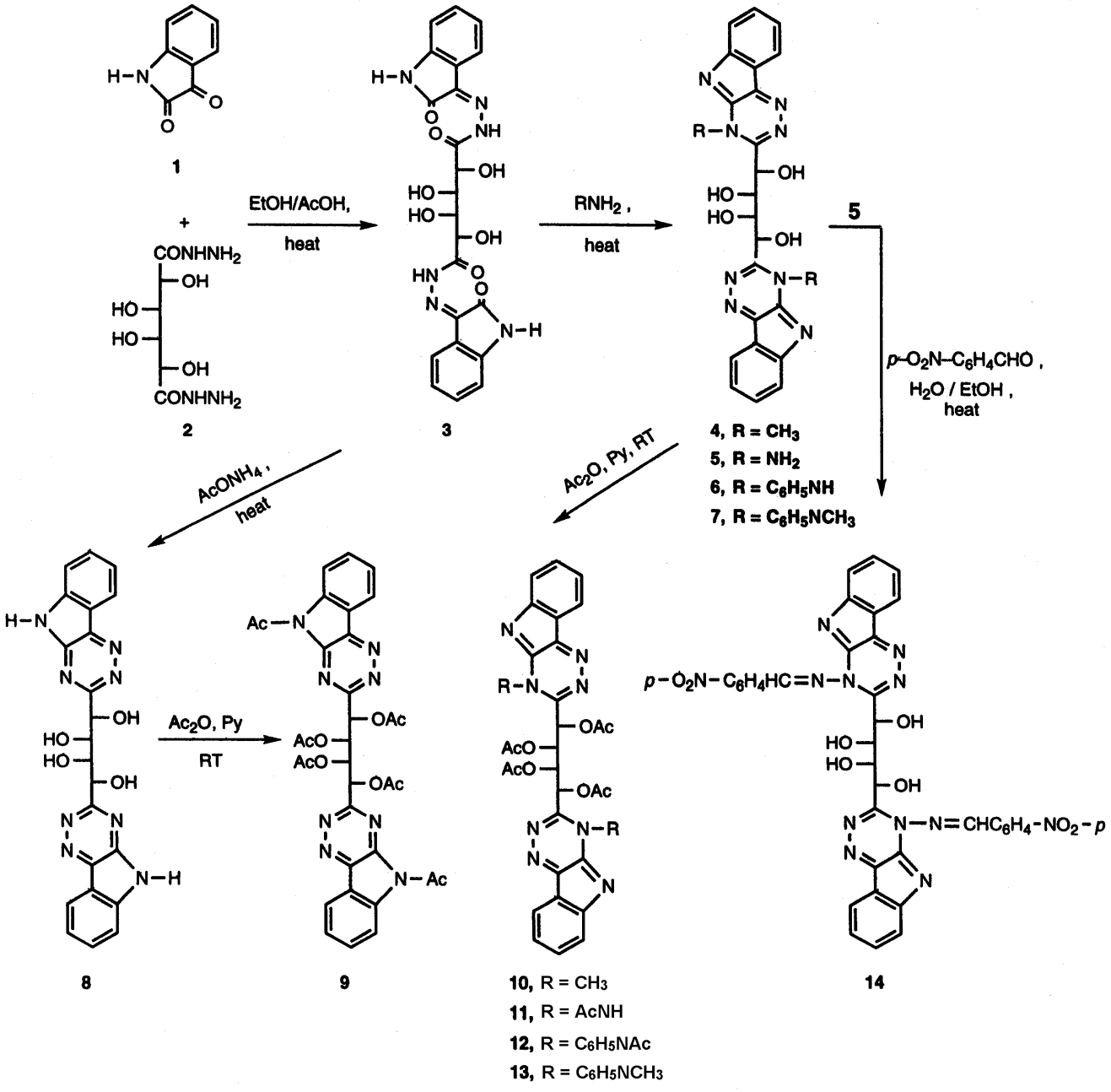
RESULTS AND DISCUSSION

Recently, we synthesized bis(2-oxo-indol-3-ylidene)-galactaric acid hydrazide (**3**) by the condensation of 2,3-dioxo-indole (**1**) with galactaric acid bis hydrazide (**2**) and studied the heterocyclization of its tetra-*O*-acetate derivative to the double headed 1,3,4-oxadiazino[5,6-*b*]indole acyclo *C*-nucleoside.[34] We report in the present investigation on the utilization of compound **3** as double headed 1,2,4-triazino-[5,6-*b*]indole acyclo *C*-nucleoside synthons. Thus, fusion of compound **3** with ammonium acetate gave a product which showed characteristic IR absorption due to overlapped OH and NH at 3287 and C=N at 1628 cm^{-1} and lacked amide absorptions and was correctly analyzed for the molecular formula $C_{22}H_{18}N_8O_4$. ^{1}H NMR of the product revealed beside the aromatic eight protons and the tetritolyl four CH protons, signals due to six exchangeable protons: two NH protons resonated as a singlet signal at δ 12.25 and tetritolyl four OH protons appeared as two doublet signals at δ 5.80 and 5.07 ppm. The product was ascribed, therfore, the 1,4-bis{*5H*-1,2,4-triazino[5,6-*b*]indol-3-yl}-*galacto*-tetritol structure

(**8**) (Scheme I).

Acetylation of compound **8** with acetic anhydride in the presence of pyridine at ambient temperature gave a single product which lacked OH and NH IR absorptions, in addition to two NH and four OH ^{1}H NMR proton signals of the parent compound. It showed OAc, CON and C=N IR absorptions as well as ^{1}H NMR proton signals attributed to the tetra-*O*-acetyl-tetritolyl chain protons (4CH and 4OAc), two N-acetyl protons in addition to the aromatic eight protons and analyzed for the molecular formula $C_{34}H_{30}N_8O_{10}$. These data are in agreement with both O-acetylation of the tetritolyl four hydroxyl groups and N-acetylation of the two heteroaryl NH protons of compound **8**. The MS of the acetylation product did not reveal its molecular ion peak, yet showed a fragment at *m/z* 335 (**15**) resulting from C1-C2 bond cleavage of the tetritolyl chain in addition to the fragments at *m/z* 241 (**16**),

Scheme I



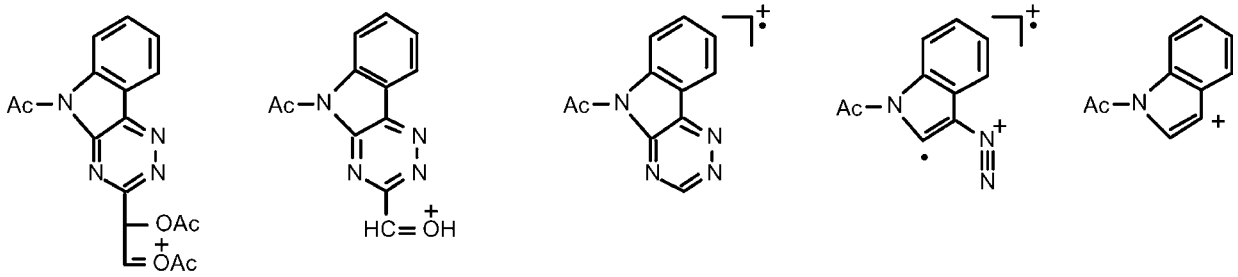
m/z 212 (**17**), *m/z* 186 (**18**) and *m/z* 158 (**19**) (Fig. 1). Fragment **16** is indicative for the carbon-carbon linkage between the tetritolyl chain and the base moiety of acyclic *C*-nucleosides,[35,36] while fragment **19** indicated that the acetylation process was involved the pyrrole ring nitrogen rather than the 1,2,4-triazine ring N2 or N4 and, consequently, the acetylation product was assigned the 1,2,3,4-tetra-*O*-acetyl-1,4-bis-{5-acetyl-1,2,4-triazino[5,6-*b*]indol-3-yl}-*galacto*-tetritol structure (**9**). Our result of preference of acetylation of the pyrrole ring nitrogen rather than the 1,2,4-triazine ring N2 or N4 of the *5H*-1,2,4-triazino[5,6-*b*]indole skeltons is in harmony with the previously reported results.[32,37] ^{13}C NMR spectrum of compound **9** showed each set of signals from the respective carbon completely overlapped with each other; thus, it revealed signals at δ 20.06, 20.12 (4OCOO*C*H$_3$), 24.09 (2NCO*C*H$_3$), 66.99, 70.84 (tetritolyl 4 carbons), 110.20 (2C6), 117.11 (2C9a), 120.09 (2C7), 122.10 (2C9), 129.43 (2C8), 138.66 (2C5a), 140.80 (2C9b), 147.28 (2C4a), 160.39 (2C3), 162.91 (2N*C*OCH$_3$), 169.36, 170.17 (4OO*C*H$_3$). These ^{13}C NMR data were assigned on the basis of comparing with the data reported for 1,2,4-triazino[5,6-*b*]indoles[5,14] and poly-*O*-acetyl-3-alditol-1-ylidenehydrazino-1,2,4-triazino[5,6-*b*]indoles.[14]

Similarly, heterocyclization of compound **3** by heating with methylamine afforded the corresponding 1,4-bis{4-methyl-1,2,4-triazino[5,6-*b*]indol-3-yl}-*galacto*-tetritol (**4**) which was further characterized with its tetra-*O*-acetate derivative **10** obtained by acetylation with acetic anhydride in the presence of pyridine at room temperature.

Subjecting compound **3** to hydrazinolysis by heating with hydrazine hydrate afforded a product which revealed IR absorptions characteristic of OH, NH$_2$ and C=N. In addition to eight aromatic proton signals, the ^{1}H NMR of the product displayed two exchangeable NH$_2$ protons as a singlet signal at δ 5.86, tetritolyl four exchangeable OH protons as two doublet signals at δ 5.41 and 5.08 and tetritolyl four CH protons as two doublet signals at δ 4.86 and 3.82 ppm. These spectral results are consistent with the 1,4-bis{4-amino-1,2,4-triazino[5,6-*b*]indol-3-yl}-*galacto*-tetritol structure **5**. The ^{13}C NMR spectrum of **5** gave characteristic signals in accordance with the assigned structure (see experimental). The MS of compound **5** showed its molecular ion peak (M^+) at *m/z* 488 (0.58%). This very low intensity may be attributed to the relative instability of **5** caused by the presence of sugar moiety in its structure.[38,39] The structure of compound **5** was also supported by its easy reaction with *p*-nitro-benzaldehyde to give the *p*-nitrobezylidene derivative **14**. In a similar fashion compound **3** underwent a condensative cyclization reaction with phenylhydrazine or 1-methyl-1-phenylhydrazine to give the double headed acyclo *C*-nucleosides **6** and **7**, respectively.

Acetylation of the acyclo *C*-nucleosides **5-7** caused acetylation of each of the tetritolyl chain hydroxyls of the three startings as well as NH of the two amino and the two phenylamino groups of **5** and **6**, respectively. Each ^{1}H NMR spectrum of the resulting tetra-*O*-acetates **11-13** revealed proton signals attributed to aromatic eight protons and the tetra-*O*-acetyl-tetritolyl chain (4CH and 4OCOCH$_3$). Compound **11** showed in addition, two exchangeable NH protons and two N-acetyl protons while each compound of **12** and **13** displayed aromatic ten protons and two methyl group protons (two NAc for compound **12** and two NCH$_3$ for compound **13**). The ^{13}C NMR spectrum of **11** showed the expected signals of its carbon skelton (see experimental).

It is notable that the ^{1}H NMR spectrum of each of the five tetra-*O*-acetates **9-13** showed its tetritolyl protons as two singlet signals with zero coupling constants confirming their centerosymmetric zigzag conformations **20** (Fig. 2) which is in agreement with the results obtained for other *galacto*-tetritol-1,4-yl acyclo *C*-nucleoides.[34,39-41]



15 *m/z* (355) **16** *m/z* (241) **17** *m/z* (212) **18** *m/z* (186) **19** *m/z* (158)

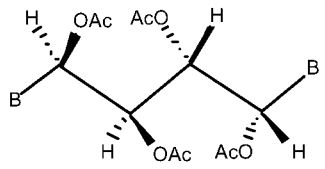
Fig. 1. Mass spectrum fragments of compound **9**.

EXPERIMENTAL

Melting points were determined on a MEL-TEMP II melting point apparatus in open glass capillaries and are uncorrected. The infrared spectra IR were recorded for potassium bromide discs on a Pye-Unicam SP1025 spectrophotometer. NMR spectra were carried out at ambient temperature (~25 °C) with a Brucker AC-250 spectrometer or with a Varian Gemini 200 spectrometer at 250 MHz using tetramethylsilane (TMS) as an internal standard. Mass spectra (MS) were preformed on a Hewlett-Packard 5995 gas chromatography-mass spectrometer system or on a Shimadzu GCMS-QP 1000 EX mass spectrometer. Homogeneity of the products and follow up of the reactions were checked by ascending thin-layer chromatography TLC on plates precoated with silica gel G (E. Merck; layer thickness 0.25 mm), used without pretreatment. All ratios of the used solvent systems were volume to volume V/V; the solvent systems used were: (A) $CHCl_3$/MeOH (1:2) and (B) $CHCl_3$/MeOH (9:1); the distance of the solvent travel was 5 cm and the spots were visualized by exposure to iodine vapour for a few minutes. Elemental microanalyses were performed at the Microanalytical Unit, Cairo University, Cairo, Egypt.

1,4-Bis{5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl}-*galacto*-tetritol (8)

Compound **3** (2 g, 4.03 mmol) was successively mixed with anhydrous ammonium acetate (0.62 g, 8.06 mmol), and the mixture was heated in a fusion tube provided with an air condenser at 170 °C for 2 h. The obtained mass was triturated with water and crystallized from H_2O-EtOH to give compound **8** as yellow crystals; yield: 66%; m.p.: 218-220 °C/dec.; TLC (A), R_f: 0.61; IR (KBr) ν_{max}: 3287 (br, OH + NH), 1628 (C=N) cm^{-1}; ^1H NMR [DMSO-d_6]: δ = 3.70, 4.53 (2d, 2H each, tetritolyl H), 5.07, 5.80 (2d, exchangeable, 2OH each), 7.14-7.18, 7.48-7.52 (2m, 4H each, Ar-H), 12.25 (s, br, exchangeable, 2NH). Anal. Calcd. for $C_{22}H_{18}N_8O_4$: C, 57.64; H, 3.93; N, 24.45. Found: C, 57.58; H, 3.96; N, 24.61.



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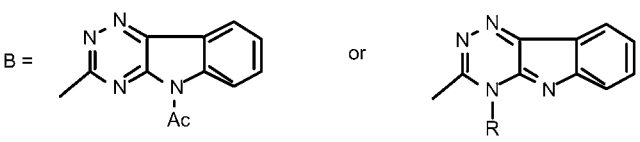

Fig. 2. Conformations of compounds **9**-**13**.

1,4-Bis{4-substituted-1,2,4-triazino[5,6-*b*]indol-3-yl}-*galacto*-tetritols (4-7)

A mixture of compound **3** (2 g, 4.03 mmol) and methylamine or the appropriate hydrazine derivatives (hydrazine hydrate, phenylhydrazine or 1-methyl-1-phenylhydrazine) (30 mL) was heated at reflux for 6 h and then evaporated under reduced presure. The obtained residue was crystallized from H_2O-EtOH. The following compounds were prepared.

1,4-Bis{4-methyl-1,2,4-triazino[5,6-*b*]indol-3-yl}-*galacto*-tetritol (4)

Yellow crystals, yield: 61%; m.p.: 232-235 °C; TLC (A), R_f: 0.60; IR (KBr) ν_{max}: 3315 (br, OH), 1602 (C=N) cm^{-1}; ^1H NMR [DMSO-d_6]: δ = 3.49 (s, 6H, $2CH_3$), 3.91, 4.55 (2d, 2H each, tetritolyl H), 5.17, 5.75 (2d, exchangeable, 2OH each), 7.13-7.16, 7.48-7.51 (2m, 4H each, Ar-H). Anal. Calcd. for $C_{24}H_{22}N_8O_4$: C, 59.26; H, 4.53; N, 23.05. Found: C, 59.09; H, 4.63; N, 23.21.

1,4-Bis{4-amino-1,2,4-triazino[5,6-*b*]indol-3-yl}-*galacto*-tetritol (5)

Yellowish white crystals, yield: 69%; m.p.: 220-222 °C/dec.; TLC (A), R_f: 0.59; IR (KBr) ν_{max}: 3280 (br, OH + NH_2), 1643 (C=N) cm^{-1}; ^1H NMR [DMSO-d_6]: δ = 3.82, 4.86 (2d, 2H each, tetritolyl H), 5.08, 5.41 (2d, exchangeable, 2OH each), 5.86 (s, br, exchangeable, $2NH_2$) 7.49-7.52, 7.78-7.84 (2m, 4H each, Ar-H); ^{13}C NMR (DMSO-d_6]: δ = 70.93, 71.23 (tetritolyl 4 carbons), 110.84 (2C6), 118.17 (2C9a), 119.13 (2C7), 122.31 (2C9), 128.71 (2C8), 137.31 (2C5a), 140.41 (2C9b), 147.93 (2C4a), 159.31 (2C3); MS *m/z* (relative intensity) 488 (M^+, 0.58), 198 (41.05), 169 (100). Anal. Calcd. for $C_{22}H_{20}N_{10}O_4$: C, 54.10; H, 4.10; N, 28.69. Found: C, 54.26; H, 4.07; N, 28.77.

1,4-Bis{4-phenylamino-1,2,4-triazino[5,6-*b*]indol-3-yl}-*galacto*-tetritol (6)

Yellowish white crystals, yield: 64%; m.p.: 258-260 °C/dec.; TLC (A), R_f: 0.58; IR (KBr) ν_{max}: 3362 (OH), 3317 (NH), 1630 (C=N) cm^{-1}; ^1H NMR [DMSO-d_6]: δ = 3.89, 4.70 (2d, 2H each, tetritolyl H), 5.17, 5.94 (2d, exchangeable, 2OH each), 7.12-7.14 (m, 4H, Ar-H), 7.49-7.58 (m, 10H, Ar-H), 7.94-7.96 (m, 4H, Ar-H), 9.09 (s, exchangeable, 2NH). Anal. Calcd. for $C_{34}H_{28}N_{10}O_4$: C, 63.75; H, 4.38; N, 21.88.

Found: C, 63.88; H, 4.27; N, 21.69.

1,4-Bis{4-(methylphenyl)amino-1,2,4-triazino[5,6-*b*]indol-3-yl}-*galacto*-tetritol (7)

Yellowish white crystals, yield: 60%; m.p.: 272-275 °C/dec.; TLC (A), R_f: 0.57; IR (KBr) ν_{max}: 3251 (br, OH), 1637 (C=N) cm^{-1}. ^1H NMR [DMSO-d_6]: δ = 3.79 (s, 6H, $2CH_3$), 3.95, 4.79 (2d, 2H each, tetritolyl H), 5.05, 5.44 (2d, exchangeable, 2OH each), 7.09-7.52 (m, 10H, Ar-H), 7.78-7.82, 8.08-8.10 (2m, 4H each, Ar-H). Anal. Calcd. for $C_{36}H_{32}N_{10}O_4$: C, 64.67; H, 4.79; N, 20.96. Found: C, 64.63; H, 4.81; N, 21.01.

1,4-Bis{4-(*p*-nitrobenzylideneamino)-1,2,4-triazino[5,6-*b*]-indol-3-yl}*galacto*-tetritol (14)

A suspension of compound **5** (1 g, 2.05 mmol) in ethanol (30 mL) was treated with a solution of *p*-nitrobenzaldehyde (0.62, 4.11 mmol) in ethanol (20 mL) containing 2 drops of CH_3COOH. The mixture was heated at reflux for 1 h and the product was filtered, washed with hot EtOH and crystallized from H_2O-EtOH to give compound **14** as pale yellow crystals; yield: 71%; m.p.: 287-290 °C/dec.; TLC (A), R_f: 0.56; IR (KBr) ν_{max}: 3296 (br, OH), 1635 (C=N) cm^{-1}; ^1H NMR [DMSO-d_6]: δ = 3.81, 4.79 (2d, 2H each, tetritolyl H), 5.17, 5.82 (2d, exchangeable, 2OH each), 7.33-7.38, 5.48-5.57 (2m, 8H each, Ar-H), Anal. Calcd. for $C_{36}H_{26}N_{10}O_8$: C, 59.50; H, 3.58; N, 19.28. Found: C, 59.58; H, 3.55; N, 19.33.

General procedure for acetylation of the acyclo *C*-nucleosides 4-8

A mixture of the appropriate compound **4-8** (2 g, 3.00-4.37 mmol), pyridine (10 mL) and acetic anhydride (30 mL) was stirred at room temperature for 48 h. The mixture was evaporated under reduced pressure and the product was crystallized from $CHCl_3$-EtOH. The folloiwng compounds were prepared.

1,2,3,4-Tetra-*O*-acetyl-1,4-bis{5-acetyl-1,2,4-triazino[5,6-*b*]indol-3-yl}-*galacto*-tetritol (9)

Pale yellow crystals, yield: 81%; m.p.: 202 °C; TLC (B), R_f: 0.62; IR (KBr) ν_{max}: 1749 (OAc), 1696 (CON), 1611 (C=N) cm^{-1}. ^1H NMR [DMSO-d_6]: δ = 1.91, 2.05 (2s, 6H each, OAc), 2.79 (s, 6H, $NCOCH_3$), 5.76, 5.92 (2s, 2H each, tetritolyl H), 7.40, 7.49 (2t, 2H each, Ar-H), 7.80, 8.09 (2d, 2H each, Ar-H); ^{13}C NMR (DMSO-d_6]: δ = 20.06, 20.12 ($4OCOO\mathit{C}H_3$), 24.09 ($2NCO\mathit{C}H_3$), 66.99, 70.84 (tetritolyl 4 carbons), 110.20 (2C6), 117.11 (2C9a), 120.09 (2C7), 122.10 (2C9), 129.43 (2C8), 138.66 (2C5a), 140.80 (2C9b), 147.28 (2C4a), 160.39 (2C3), 162.91 ($2N\mathit{C}OCH_3$), 169.36, 170.17 ($4OO\mathit{C}CH_3$); MS *m/z* (relative intensity) 355 (33.70), 241 (9.20), 212 (4.10), 186 (2.07), 169 (100), 158 (9.92). Anal. Calcd. for $C_{34}H_{30}N_8O_{10}$: C, 57.47; H, 4.23; N, 15.78. Found: C, 57.60; H, 4.12; N, 15.90.

1,2,3,4-Tetra-*O*-acetyl-1,4-bis{4-methyl-1,2,4-triazino[5,6-*b*]indol-3-yl}-*galacto*-tetritol (10)

Pale yellow crystals, yield: 79%; m.p.: 240 °C; TLC (B), R_f: 0.63; IR (KBr) ν_{max}: 1747 (OAc), 1626 (C=N) cm^{-1}. ^1H NMR [DMSO-d_6]: δ = 2.17, 2.25 (2s, 6H each, OAc), 3.68 (s, 6H, NCH_3), 5.08, 5.59 (2s, 2H each, tetritolyl H), 7.49-7.52, 7.74-7.77 (2m, 4H each, Ar-H). Anal. Calcd. for $C_{32}H_{30}N_8O_8$: C, 58.72; H, 4.59; N, 17.13. Found: C, 58.59; H, 4.63; N, 17.18.

1,2,3,4-Tetra-*O*-acetyl-1,4-bis{4-acetamido-1,2,4-triazino-[5,6-*b*]indol-3-yl}-*galacto*-tetritol (11)

Colorless crystals, yield: 78%; m.p.: 258 °C; TLC (B), R_f: 0.61; IR (KBr) ν_{max}: 3218 (NH), 1751 (OAc), 1678 (CON), 1624 (C=N) cm^{-1}. ^1H NMR [DMSO-d_6]: δ = 1.98, 2.04 (2s, 6H each, OAc), 2.98 (s, 6H, 2NAc), 5.09, 5.49 (2s, 2H each, alditolyl H), 7.49-7.52, 7.75-7.77 (2m, 4H each, Ar-H), 8.26 (s, br, exchangeable 2NH); ^{13}C NMR (DMSO-d_6]: δ = 20.10, 20.71 ($4OCOO\mathit{C}H_3$), 24.13 ($2NCO\mathit{C}H_3$), 68.14, 68.08 (tetritolyl 4 carbons), 110.73 (2C6), 117.53 (2C9a), 119.99 (2C7), 122.04 (2C9), 129.01 (2C8), 138.39 (2C5a), 140.31 (2C9b), 147.61 (2C4a), 159.47 (2C3), 163.41 ($2N\mathit{C}OCH_3$), 169.71, 170.34 ($4OO\mathit{C}CH_3$). Anal. Calcd. for $C_{34}H_{32}N_{10}O_{10}$: C, 55.14; H, 4.32; N, 18.92. Found: C, 55.24; H, 4.22; N, 19.01.

1,2,3,4-Tetra-*O*-acetyl-1,4-bis{4-(acetylphenyl)amino-1,2,4-triazino[5,6-*b*]indol-3-yl}-*galacto*-tetritol (12)

Colorless crystals, yield: 71%; m.p.: 262 °C; TLC (B), R_f: 0.58; IR (KBr) ν_{max}: 1754 (OAc), 1675 (NCO), 1595 (C=N) cm^{-1}. ^1H NMR [DMSO-d_6]: δ = 1.91, 2.19 (2s, 6H each, OAc), 2.59 (2s, 6H, $NCOCH_3$), 5.21, 5.79 (2s, 2H each, alditolyl H), 6.94-6.99 (m, 4H, Ar-H), 7.13-7.17 (m, 10H, Ar-H), 7.48-7.51 (m, 4H, Ar-H). Anal. Calcd. for $C_{46}H_{40}N_{10}O_{10}$: C, 61.88; H, 4.48; N, 15.70. Found: C, 61.97; H, 4.36; N, 15.83.

1,2,3,4-Tetra-*O*-acetyl-1,4-bis{4-(methylphenyl)amino-1,2,4-triazino[5,6-*b*]indol-3-yl}-*galacto*-tetritol (13)

Colorless crystals, yield: 72%; m.p.: 233 °C; TLC (B), R_f: 0.60; IR (KBr) ν_{max}: 1754 (OAc), 1615 (C=N) cm^{-1}. ^1H NMR [DMSO-d_6]: δ = 1.97, 2.19 (2s, 6H each, OAc), 3.73 (s, 6H, NCH_3), 5.23, 5.56 (2s, 2H each, alditolyl H), 7.12-7.46 (m, 4H, Ar-H), 7.49-7.58 (m, 10H, Ar-H), 7.94-7.99 (m, 4H,

Ar-H), Anal. Calcd. for $C_{44}H_{40}N_{10}O_8$: C, 63.16; H, 4.79; N, 16.75. Found: C, 63.22; H, 4.81; N, 16.84.

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